

## Transient Sympathovagal Imbalance Triggers "Ischemic" Sudden Death in Patients Undergoing Electrocardiographic Holter Monitoring

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**Objectives.** The aim of this study was to investigate the relation between "ischemic" sudden death (arrhythmic death preceded by ST segment shift) and autonomic nervous system activity.

**Background.** Mechanisms precipitating sudden death are poorly known despite the importance of detecting functional factors that may contribute to such a fatal event.

**Methods.** We analyzed the tapes of eight patients (seven men and one woman with a mean age of  $66 \pm 8$  years) who had ischemic sudden death during ambulatory electrocardiographic (Holter) monitoring. Four patients had unstable and four had stable angina; none was taking antiarrhythmic drugs. Twenty patients with angina and transient myocardial ischemia during Holter monitoring served as control subjects. Arrhythmias, ST segment changes and heart rate variability were analyzed by a computerized interactive Holter system.

**Results.** Five patients had ventricular tachyarrhythmias (ventricular fibrillation in three, ventricular tachycardia in two), and three had bradyarrhythmias (atrioventricular block in two, sinus

arrest in one) as the terminal event; all eight patients showed ST segment shift (maximal change  $0.46 \pm 0.16$  mV; with ST elevation in two) that occurred  $41 \pm 34$  min (mean  $\pm$  SD) before sudden death. The standard deviation of normal RR intervals (SDNN) was  $89 \pm 33$  ms during the  $10 \pm 6$  h of Holter monitoring; 5 min before the onset of the fatal ST shift, SDNN measurements were significantly lower than during the initial 5-min period ( $48 \pm 10$  vs.  $29 \pm 9$  ms;  $p = 0.002$ ). In control patients, the SDNN was  $102 \pm 39$  ms during Holter monitoring, whereas it measured  $56 \pm 30$  ms 5 min before the most significant episode of ST shift ( $p < 0.01$  vs.  $129 \pm 9$  ms in the group with sudden death).

**Conclusions.** Autonomic dysfunction, as detected by a marked decrease in heart rate variability, is present in the period (5 min) immediately preceding the onset of the ST shift precipitating ischemic sudden death. These data suggest that sympathovagal imbalance may trigger fatal arrhythmias during acute myocardial ischemia, thus resulting in sudden death.

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The occurrence of sudden death is the leading unfavorable outcome in the natural history of ischemic heart disease (1). More than two thirds of these deaths can be attributed to the occurrence of malignant ventricular arrhythmias (2), but it is not clear whether we can identify patients at high risk for sudden death or improve survival with antiarrhythmic therapy (3). Uncertainties are mainly due to poor knowledge of the mechanisms underlying the pathophysiology of the disease. Data from experimental research indicate that both acute myocardial ischemia (4) and autonomic nervous system dysfunction (5) may facilitate the occurrence of fatal arrhythmias. Low heart rate variability has also been found (6) to be a risk factor for sudden cardiac death after myocardial infarction. The attenuated overall variability is thought to be due to an

autonomic imbalance caused by high sympathetic activity or concomitant low vagal activity, or both (7). However, the mechanism by which sympathovagal imbalance may precipitate sudden death in humans is not clear. The best source of information comes from the tapes of patients who died during ambulatory electrocardiographic (ECG) Holter monitoring (8). To date, little is known about the relation among the presence of autonomic nervous system dysfunction, the incidence of myocardial ischemia and the occurrence of sudden death. The present study investigated the risk implication of heart rate variability in patients with coronary artery disease who had "ischemic" sudden death—that is, arrhythmic death preceded by ST segment shift—during Holter monitoring.

### Methods

All patients with an anginal syndrome and sudden cardiac death (9) during Holter monitoring were eligible for this study. Twenty patients, gender- and age-matched, with angina and

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transient myocardial ischemia, but no life-threatening ventricular arrhythmias (Lown class <4) during 24-h Holter monitoring, served as control subjects; these subjects had no cardiac event within 1 month of Holter recording. No patient had previous Q wave myocardial infarction or signs or symptoms of heart failure.

Holter tapes were obtained from three hospitals located in Bologna from 1988 to 1994; accurate diaries were kept by all patients. Sudden death was defined as "ischemic" if the fatal arrhythmia was preceded by transient significant ST segment changes. Tapes were analyzed by a computer-assisted Holter system for heart rate variability calculations. (Accuplus 363, Del Mar Avionics). Recordings were reviewed by an interactive operator-assisted mode ("confirm" scanning option) that allows labeling of each ventricular complex. Arrhythmic events and ST segment trends were obtained to document the fatal arrhythmia and transient ST segment changes suggestive of myocardial ischemia (ST shift  $>0.15$  mV lasting  $>2$  min). Only two-channel ECG recordings of adequate quality (that is, with  $>80\%$  of correctly labeled normal beats) were used; artifacts, ectopic beats and periods with significant ST segment changes were removed by RR calculations. Time domain measurements of heart rate variability indexes were assessed by an automatic program (Beta SHR.V, 1994).

Heart rate range was analyzed between 40 and 385 beats/min; the maximal allowable beat to beat RR variation was 20%. Measurements were obtained by active analysis of 5 and 60-min time segments ("epochs"). All normal RR (NN) intervals and their standard deviations (SD) were used to calculate five variables that have been shown (10,11) to be related to changes in sympathovagal balance: the SD of normal NN intervals (SDNN); the mean of SDs for 5-min segments (SDNN index); the average of mean SDs for 5-min segments (SDANN index); the percent difference of successive normal beats differing by  $>50$  ms (pNN50); and the root-mean-square of SDs (rMSSD). For analytic purposes, the mean values of two heart rate variability indexes (SD of NN intervals and percent of NN  $>50$  ms) were measured in patients with sudden death as follows: a) for the total Holter recording; b) in the initial 1 h (epoch 1), including the last 5 min (epoch 2); c) 1 h (epoch 3), including the last 5 min (epoch 4), before the onset of ST segment shift, whether or not ST segment change led to sudden death. The remaining variables—SDNN index, SDANN index and rMSSD—were calculated in the overall monitoring period and in epochs 1 and 3. In the control group, the SD of NN intervals and the percent of NN  $>50$  ms were measured during the overall 24-h Holter recording and 1 h and 5 min before each episode of ST segment shift (epoch 3 and epoch 4, respectively).

**Statistical analysis.** Statistical analysis within a group was performed by the Student paired *t* test. Comparison between the two groups was assessed by Mann-Whitney-Wilcoxon rank sum test; *p* values  $< 0.05$  were considered significant.

**Table 1.** Clinical Data for Patients With Sudden Death

Pt No.	Age (yr)/ Gender	Angina	Treatment
1	78/M	Post MI	N + ACE
2	68/F	Stable	N + CB
3	55/M	Stable	N
4	55/M	Recent Onset	ACE
5	65/M	Unstable	N + CB
6	67/M	Stable	N + CB
7	74/M	Stable	N + CB
8	70/M	Unstable	N

ACE = angiotensin-converting enzyme inhibitor; CB = calcium channel blocker; F = female; M = male; MI = myocardial infarction; N = nitrate; Pt = patient.

## Results

**Patients with ischemic sudden death.** Eight patients were selected for final analysis: seven men, and one woman with a mean age of  $66 \pm 8$  years. Two additional patients who met the study criteria were excluded: one with paroxysmal atrial fibrillation and the other, a 83-year old woman being treated with beta-adrenergic blocking agents. Five of the eight patients underwent ambulatory Holter monitoring during daily life; the other three underwent Holter monitoring during a hospital stay. All patients had a history of angina pectoris: four with unstable angina (one with recent onset effort angina) and four with chronic stable effort angina (one with a previous non-Q wave myocardial infarction). No patient had a history of diabetes or was taking antiarrhythmic drugs, including digoxin or a beta-blocker. Clinical data and drug treatment are reported in Table 1. The mean duration  $\pm$  SD of ECG Holter recordings was  $10 \pm 6$  h (range 3 to 23). Recorded channels were CM<sub>1</sub> in all eight patients, CM<sub>2</sub> in seven and modified aVF in one patient who had shown ST segment depression in the inferior leads during exercise testing. All patients showed ventricular ectopic beats during monitoring; only one patient had frequent ( $>10$ /h) and complex (couplets) ventricular ectopic beats. Sudden death was due to a ventricular tachyarrhythmia in five patients (ventricular fibrillation in three and sustained ventricular tachycardia degenerating into fibrillation in two); the other three patients showed bradyarrhythmias (advanced atrioventricular block in two and slow idioventricular rhythm followed by sinus arrest in one patient). Six of the eight patients reported chest pain before dying. All patients exhibited ST segment shift during ECG monitoring: ST depression (maximal  $0.37 \pm 0.20$  mV) occurred in six and ST elevation ( $0.52 \pm 0.18$  mV) in two. The mean duration of fatal ST shift episodes was  $41 \pm 34$  min (range 10 to 98). Table 2 shows Holter data. The mean heart rate at the onset of ST shift was  $77 \pm 14$  beats/min versus  $74 \pm 6$  beats/min during overall monitoring (*p* = NS). In four patients seven additional ischemic episodes occurred during ECG monitoring  $\pm 1$  h before the onset of ischemic sudden death; such ST shifts (lasting  $43 \pm 39$  min,  $0.29 \pm 0.11$  mV) were defined as nonfatal episodes of transient myocardial ischemia and were used for analytic purposes.

**Table 2.** Holter Electrocardiographic Data for Patients With Sudden Death

Pt No.	Duration of Monitoring (h)	Fatal Arrhythmia	ST Segment Shift/Anginal Pain	Duration/Max ST Segment (min/mV)	Episodes of ST Segment Shift (no.)
1	3	VF	↓/No	20/0.20	1
2	10	VF	↓/Yes	35/0.41	2
3	9	AV block	↑/Yes	13/0.40	1
4	23	VT	↓/No	88/0.71	4
5	13	VT	↓/Yes	44/0.37	2
6	7	VF	↓/Yes	98/0.47	2
7	13	Sinus arrest	↑/Yes	21/0.65	1
8	5	AV block	↓/Yes	10/0.49	1
Mean	9			41/0.46	1.8
±SD	6			34/0.16	1.0

AV = atrioventricular; MAX = maximal; Pt = patient; VF = ventricular fibrillation; VT = ventricular tachycardia; ↓ = depression; ↑ = elevation.

**Control group.** The control group comprised 20 patients (16 men and 4 women with a mean age of  $67 \pm 6$  years); 11 had stable and 9 had unstable angina. Thirteen of these 20 subjects underwent ambulatory 24-h Holter monitoring during daily life, 7 during a hospital stay. None was taking antiarrhythmic drugs, including beta-blockers. Eighteen patients were being treated with nitrates and 15 with calcium channel blockers; the prevalence of such antianginal medications was similar ( $p = NS$ ) to that in the group with sudden death. In the control subjects, the episode of ST segment shift that was most prolonged or most severe, or both, was selected for comparison. In four subjects the most prolonged and the most severe episodes did not coincide. Thus, 24 episodes of ST segment shift during Holter monitoring in 20 subjects were chosen for analysis. Anginal pain was associated with ST shift in 15 of the 24 episodes. Eighteen were episodes of ST segment depression (maximum  $0.32 \pm 0.10$  mV), and 6 of ST elevation ( $0.44 \pm 0.28$  mV). The mean duration of such episodes was  $30 \pm 26$  min (range 5 to 89). All of these data were similar ( $p = NS$ ) to those obtained in the sudden death group. The mean heart rate at the onset of ST shift was  $85 \pm 15$  beats/min, whereas it was  $73 \pm 8$  beats/min during 24-h Holter monitoring ( $p < 0.001$ ).

**Heart rate variability analysis.** *Patients with ischemic sudden death.* The mean RR interval in the eight patients with ischemic sudden death was  $767 \pm 89$  ms during the overall ECG monitoring period. Time domain measurements of heart rate variability were as follows: The total SD of NN intervals was  $89 \pm 33$  ms, whereas it measured  $72 \pm 12$  and  $48 \pm 10$  ms in the initial epochs 1 and 2, respectively. The SD of NN intervals was lower before the occurrence of ischemic sudden death:  $58 \pm 15$  ms ( $p < 0.03$ ) in epoch 3 and  $29 \pm 9$  ms ( $p = 0.002$ ) in epoch 4 (i.e., 5 min before the onset of the fatal ST segment shift). Trends of the RR interval and its SD in a patient with ischemic sudden death are reported in Figure 1. Furthermore, the lowest value of SD of NN intervals, as obtained in the total Holter recording, was not statistically different from the epoch 4 measurements ( $21 \pm 10$  vs.  $29 \pm 9$  ms;  $p = NS$ ). Values for the remaining variables of sympathovagal balance (Table 3), referring to overall and 1-h peri-

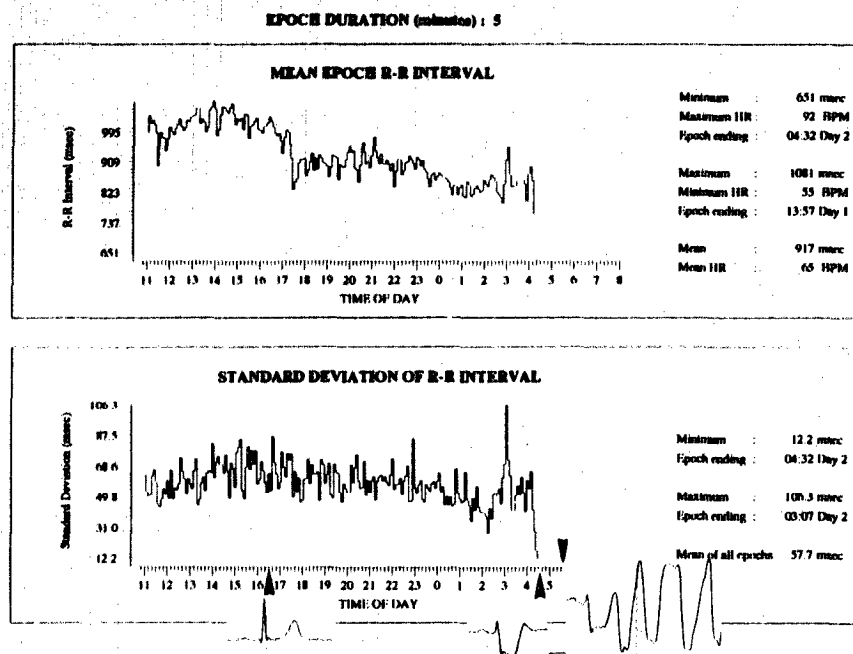
ods, gave similar results. Parasympathetic variables of heart rate variability were slightly lower before the ST shift leading to sudden death than in the initial time segments: The percent of NN  $> 50$  ms was  $8.3 \pm 6.3$  vs.  $7.4 \pm 6.7\%$  in epoch 1 versus epoch 3 ( $p = NS$ ), whereas it measured  $8.9 \pm 5.2$  versus  $6.2 \pm 4.1\%$  in epoch 2 versus epoch 4 ( $p < 0.01$ ). Similar data were observed with the root-mean-square of SDs:  $32 \pm 11$  versus  $30 \pm 9$  ms in epoch 1 and epoch 3, respectively ( $p = NS$ ). Heart rate variability measurements are shown in Table 3. The three patients with bradyarrhythmic death showed persistent and markedly low values of percent of NN  $> 50$  ms during the overall ECG monitoring periods (range 0 to 2.5%).

**Control group.** In the control subjects, heart rate variability was analyzed before 24 episodes of ST shift. The SD of NN intervals during 24 h was  $102 \pm 39$  ms, whereas it measured  $67 \pm 25$  ms in epoch 3 and  $56 \pm 30$  ms in epoch 4 ( $p = NS$ ), respectively, 1 h and 5 min before the most significant episode of ST shift. Parasympathetic variables during overall monitoring (percent of NN  $> 50$  ms:  $6.6 \pm 6.2\%$ ) were similar ( $p = NS$ ) to those obtained in epoch 3 ( $7.2 \pm 5.5\%$ ) or epoch 4 ( $5.4 \pm 6.8\%$ ) before the onset of selected ST shift episodes.

**Comparison between the two groups.** The SD of NN intervals was similar in the overall ECG monitoring periods ( $p = NS$ ). Analysis of epoch 4 (i.e., 5 min before the ischemic episodes) showed a marked difference between the two groups: the SD of NN intervals was  $29 \pm 9$  ms in the sudden death group versus  $56 \pm 30$  ms in control subjects ( $p < 0.01$ ). In the four patients with sudden death who had seven additional nonfatal ischemic episodes, measurements 5 min before the onset of ST segment changes differed significantly ( $p < 0.01$ ) from those of epoch 4:  $60 \pm 9$  versus  $35 \pm 12$  ms. Figure 2 compares the values of SD of NN intervals between the patients with ischemic sudden death and control subjects.

## Discussion

The results of this study indicate that a decrease in heart rate variability occurs in the short time period—5 min—preceding ischemic sudden death in patients with an anginal



**Figure 1:** Diagram showing the original trends of the RR interval (upper panel) and its SD for 5-min epochs (lower panel), as obtained by heart rate variability calculations, in a patient with unstable angina with ischemic sudden death. Arrowheads indicate electrocardiographic strips generated by Holter recordings at baseline, during ST segment depression and at the onset of ventricular tachycardia, respectively. The decrease in the SD of NN intervals (lower panel) occurs just before the onset of fatal ischemic changes.

syndrome undergoing Holter monitoring. Notably, a decrease of SDNN preceded 95% (37 of 39) of all ischemic episodes, in both the sudden death and control groups. Sympathovagal imbalance, as expressed by SD of NN intervals, shows dramatic

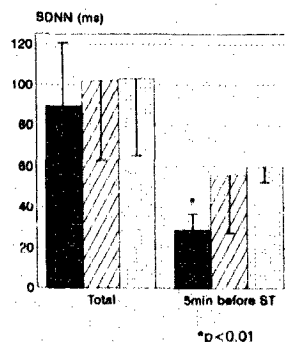
changes before the ST shift leading to sudden death, compared with findings in patients with transient myocardial ischemia as well but without death or malignant arrhythmias. All but 1 of the 8 patients who died suddenly had an SD of NN intervals value <35 ms 5 min before the onset of myocardial ischemia,

**Figure 2.** Values for the standard deviation of normal RR intervals (SDNN) are reported for control subjects (hatched bars, 24 ischemic episodes in 20 patients) and patients with ischemic sudden death (solid bars, 8 fatal episodes in 8 patients; dotted bars, 7 nonfatal episodes in 4 of the 8 patients). At left, values refer to overall recordings; at right, values refer to those obtained 5 min before ST shift. The SDNN is significantly reduced at the onset of fatal ischemic episodes when compared either with that recorded in nonfatal episodes or before ST shifts in control subjects.

**Table 3.** Heart Rate Variability Data For Patients With Sudden Death

Epoch	SDNN (ms)	SDANN (ms)	pNN50 (%)	rMSSD (ms)
All	89 ± 33	105 ± 24	10.0 ± 5.4	31 ± 11
1 (1 h)	72 ± 12	85 ± 36	8.3 ± 6.3	32 ± 11
3 (1 h before ISD)	58 ± 15	51 ± 22	7.4 ± 6.7	30 ± 9
2 (5 min)	48 ± 10		8.9 ± 5.2	
4 (5 min before ISD)	29 ± 9		6.2 ± 4.1	

\*p < 0.001, †p < 0.01, ‡p < 0.03. Data are expressed as mean value ± SD. ISD = ischemic sudden death; pNN50 = percent difference of normal beats differing by ≥50 ms; rMSSD = root-mean square of standard deviations (SD); SDANN = average of mean SDs for 5-min segments; SDNN = SD of normal NN intervals.



whereas 90% of control subjects (18 of 20) had higher values. Further analysis of four patients with sudden death who had nonfatal episodes of ST shift before dying confirmed these findings: The SD of NN intervals before nonfatal ST shifts was higher (60 vs. 29 ms) than that observed in ischemic episodes related to sudden death.

**Relation between heart rate variability and ST changes in sudden death.** All of the ventricular tachyarrhythmias leading to sudden death occurred in patients with ST depression, whereas bradyarrhythmias were mostly (two of three) preceded by ST elevation; the decrease of SD of NN intervals did not differ between these two subsets of patients. A relation between ST shifts and type of arrhythmias has been described only in preliminary reports (12). In our study, patients with bradyarrhythmias showed persistently low levels of percent of NN >50 ms, whereas those with ventricular tachyarrhythmias had a sudden decrease in this index before fatal ST shifts. This finding suggests that different patterns of sympathovagal imbalance may precipitate different manifestations of ischemia-induced arrhythmic sudden death.

The relation between heart rate variability and sudden death is still under scrutiny. A previous investigation (13) demonstrated in a small group of patients with coronary artery disease who had sudden death during Holter monitoring that mean heart rate variability was lower than that in normal subjects. In contrast, a recent study (14) in a similar cohort of patients showed no significant reduction of heart rate variability before ventricular fibrillation compared with that in patients with nonsustained ventricular tachycardia. However, the two studies examined substantially different control groups. Apparent discrepancies could also be explained by the fact that in patients with coronary artery disease, ventricular tachyarrhythmias do not necessarily occur in the presence of transient myocardial ischemia (15). No data exploring heart rate variability are available with regard to the prevalence of ST shift in patients with life-threatening arrhythmias. Therefore, the present study specifically investigated the subset of patients (10% to 30% in previous studies) (8,12) with "ischemic" sudden death. These findings definitely demonstrate that sympathovagal imbalance does indeed play a significant role in the pathogenesis of malignant arrhythmias.

**Mechanisms underlying decreased heart rate variability.** Detection of any factor that has predictive value for ischemia-related malignant arrhythmias is recommended. Indeed, the concomitance of multiple pathogenetic factors seems to be mandatory for precipitation of sudden death (9). Among these factors, autonomic nervous system activity has been suggested (16,17) to be an independent risk factor for sudden death after myocardial infarction or after coronary angiography. However, the low values of SD of NN intervals observed in the present study before ischemic sudden death (<43 ms, which is similar to those reported in high risk patients) (6) cannot be attributed to anatomic postinfarction damage of cardiac sympathetic fibers, as documented in experimental investigations (18). Conversely, the value of total SD of NN intervals observed in our study—89 ms—is similar to that obtained in patients with

coronary artery disease (19). This finding suggests that sympathovagal imbalance may have only a functional mechanism, because patients with ischemic sudden death did not show any cardiovascular disorder known to reduce heart rate variability, such as recent infarction, heart failure or diabetes (20). Also, patients with sudden death, as well as control subjects, were taking cardioactive drugs, such as calcium channel blockers or nitrates, that have no or little effect on heart rate variability (21). Thus, the observed decrease in SD of NN intervals occurring in the 5 min before fatal ST segment changes has pathogenetic implications, indicating that transient myocardial ischemia may trigger malignant arrhythmias when superimposed on transient autonomic dysfunction.

**Conclusions.** The balance between sympathetic and vagal activities has been explored by means of heart rate variability analysis; both a reduction of vagal output and an increase in adrenergic drive may be deleterious and lead to ventricular arrhythmogenesis (7). Our data confirm the role of sympathovagal imbalance in patients with sudden death, as obtained by time domain heart rate variability analysis; unfortunately, this technique does not allow measurements of the two specific components of autonomic activity (22). The use of frequency domain heart period variability would better clarify the importance of sympathetic versus parasympathetic activity, as detected by spectral analysis of low versus high frequencies (23). In conclusion, measurements of autonomic nervous system activity seem to be useful in patients with transient myocardial ischemia. Further prospective studies are needed to define the predictive value of such findings, because of the potential high risk for malignant arrhythmias.

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